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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,598	04/16/2004	Paolo Sarmientos	15702-003001	1200

26161 7590 06/06/2005

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BOSTON, MA 02110

EXAMINER

ROBINSON, HOPE A

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/826,598	SARMIENTOS ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 06 December 2004.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-24 is/are pending in the application.
- 4a) Of the above claim(s) 15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 12-14, 16-19 and 21-23 is/are rejected.
- 7) ☒ Claim(s) 7-11, 20 and 24 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 April 2004 is/are: a) ☐ accepted or b) ☒ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>10/29/04</u> . | 6) <input type="checkbox"/> Other: _____ |

AS

DETAILED ACTION

Application Status

1. Applicant's election with traverse of Group I (claims 1-14 and 16-24) is acknowledged. The traversal is on the grounds that claim 15 should be rejoined with Group I as the claim is directed to a M5 pro-UK protein. This argument is not persuasive because Group I is directed to a method of preparing the pro-UK and the MPEP states that if the product can be shown to be of use in a materially different process, the restriction requirement is proper, which is set forth the office action mailed on November 3, 2004. Therefore, the restriction requirement is proper and is final.
2. Claims 1-24 are pending. Claims 1-14 and 16-24 are under examination. Claim 15 is withdrawn from further consideration pursuant to 37 CFR 1.12(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim.

Drawing

3. The drawings are objected to because Figure 3 is missing a portion of the plasmid presented and Figure 4 is blurry. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being

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amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Duplicate Claims, Warning

4. Applicant is advised that should claims 1-3 and 8 be found allowable, claims 21-24 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Correction of the above is required.

Claim Objection

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5. Claims 7-11, 20 and 24 are objected to because of the following informalities:

Claims 7-11, 20 and 24 are objected to because the claims depend from a rejected based claim.

Correction of the above is required.

Information Disclosure Statement

6. The Information Disclosure Statement filed on October 29, 2004 has been received and entered. The references cited on the PTO-1449 Form have been considered by the examiner and a copy is attached to the instant Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 12-14 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

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The claims are directed to a method to produce a pro-UK mutant utilizing a T7 promoter and Shine-Dalgarno sequence. The specification on page 2 disclose that the main parameters of the invention is a new method using a Phage T7 promoter, a Shine-Dalgarno sequence and an *E. coli* type B strain BL21/DE3 RIL as the host cell for the expression of a mutant human pro-UK gene that encodes these pro-UK mutants. The claims are also directed to a composition comprising the mutant made in the method and to packaging with directions said composition for use in administering a bolus to a patient exhibiting symptoms of a stroke or a heart attack (see for example claim 19). The specification provides no disclosure of a kit or demonstrate a method of treating stroke or a heart attack with the mutant made. Absent guidance/direction with regard to how to use the claimed composition in a medicament and showing of said composition being effective to treat the claimed diseases, the instant specification lacks adequate written description and one of skill in the art would have to conclude that at the time of filing applicant was not in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention. The claim is indefinite for the recitation of "containing a sufficient amount of kanamycin" as it is unclear what quantity of kanamycin is considered to be a "sufficient amount".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103 (a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103 (c) and potential 35 U.S.C. 102 (f) or (g) prior art under 35 U.S.C. 103 (a).

10. Claims 1, 5 and 21 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Orsini et al. (Eur. J. Biochem, vol. 195, pages 691-697) in view of Yuming et al. (Chinese Journal of Biotechnology, vol. 13(4), pages 233-8, 1997).

Orsini et al. teach a mutated pro-UK expressed in *E. coli* B strain having a Shine Dalgarno sequence (claims 1 and 21, see pages 592 and 593) utilizing a tryptophan promoter. Orsini et al. is silent on a T7 promoter. Further, Orsini et al. teach a two step fermentation process (claim 5, see pages 693-694). In-so-far-as Orsini et al. does not teach the T7 promoter, Yuming et al. teach a pro-UK expressed in *E. coli* BL21(DE3)pLyss under the control of the T7 promoter (page 1215). In view of the foregoing, a method of preparing a pro-UK mutant polypeptide by inserting the nucleic acid encoding said protein into an expression plasmid comprising a T7 promoter and Shine-Dalgarno sequence and transforming a *E. coli* type B strain bacteria is obvious (claims 1 and 21).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have a method of preparing a pro-UK mutant polypeptide by inserting the nucleic acid encoding said protein into an expression plasmid comprising a T7 promoter and Shine-Dalgarno sequence and transforming *E. coli* type B strain bacteria, because Orsini et al. teach a mutated pro-UK expressed in *E. coli* B strain having a Shine Dalgarno sequence utilizing a tryptophan promoter. Although the reference is silent on "a T7 promoter", one of ordinary skill in the art knows that the promoter controls growth and allows for high level expression and Yuming et al. teach a pro-UK expressed in *E. coli* BL21(DE3)pLysS under the control of the T7 promoter. One of ordinary skill in the art would be motivated to combine the teachings of the reference because Yuming et al. teach that the expression level of the recombinant pro-UK attained up to 15% of the total bacterial proteins. Further, it is

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obvious to modify the method of Orsini et al. by substituting the T7 promoter of Yuming with a reasonably expectation of success, because Yuming et al. teach that the previous expression level of pro-UK was 2% and that under the control of the T7 promoter a high level of expression is achieved (see page 238). Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

11. Claims 1-5, 19 and 21-23 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Orsini et al. (Eur. J. Biochem, vol. 195, pages 691-697) in view of Ning et al. (Circulation Research, vol. 90 (7), pages 757-763, 2002) and Yuming et al. (Chinese Journal of Biotechnology, vol. 13(4), pages 233-8, 1997).

Orsini et al. teach a mutated pro-UK expressed in *E.coli* B strain having a Shine Dalgarno sequence (claims 1 and 21, see pages 592 and 593) utilizing a tryptophan promoter. Further, Orsini et al. teach a two step fermentation process (claim 5, see pages 693-694). Orsini et al. is silent on a T7 promoter and the mutation Lys300-His. Ning et al. teach pro-UK expressed in *E.coli* B strain subjected to site directed mutagenesis producing a mutation of Lys300-His (claims 3 and 23) that is a flexible loop mutant (claims 2 and 22). As Ning et al. teach a M5 pro-UK mutant, absent evidence to the contrary, claim 4 is obvious as the claim recites properties of the mutant. Further Ning et al. teach a purified culture of *E coli* (claim 19). In-so-far-as Orsini et al. and Ning et al. do not teach the T7 promoter, Yuming et al. teach a pro-UK expressed in *E. coli* BL21(DE3)pLyss under the control of the T7 promoter (page 1215).

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Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have a method of preparing a pro-UK mutant polypeptide by inserting the nucleic acid encoding said protein into an expression plasmid comprising a T7 promoter and Shine-Dalgarno sequence and transforming *E. coli* type B strain bacteria, because Orsini et al. teach a mutated pro-UK expressed in *E. coli* B strain having a Shine Dalgarno sequence utilizing a tryptophan promoter and Ning et al. teach a mutant with the mutation Lys300-His with flexible loop. Although the Orsini et al. and Ning et al. references are silent on "a T7 promoter", one of ordinary skill in the art knows that the promoter controls growth and allows for high level expression and Yuming et al. teach a pro-UK expressed in *E. coli* BL21(DE3)pLysS under the control of the T7 promoter. One of ordinary skill in the art would be motivated to combine the teachings of the reference because Yuming et al. teach that the expression level of the recombinant pro-UK attained up to 15% of the total bacterial proteins. Further, it is obvious to modify the method of Orsini et al. by substituting the T7 promoter of Yuming with a reasonably expectation of success, because Yuming et al. teach that the previous expression level of pro-UK was 2% and that under the control of the T7 promoter a high level of expression is achieved (see page 238). Thus, the claimed invention was obvious to make and use at the time it was made and was *prima facie* obvious.

Conclusion

12. No claims are allowable.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday from 9:00 a.m. to 6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner


5/31/05